PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
REG 720-PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/ 17173	22/06/2000	07/07/1999
Applicant		
REGENERON PHARMACEUTICALS INC		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   USE OF RAS INHIBITORS FOR INHIBITING MUSCLE ATROPHY

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-5,7-38,40-41 relate to an extremely large number of possible compounds/methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds explicitly mentioned in the claims 6 and 39, (PD98059 and farnesyl transferase) and for the relationship between the mechanism of action disclosed in the application and skeletal muscle atrophy.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	COOLICAN SHARON A ET AL: "The mitogenic and myogenic actions of insulin-like growth factors utilize distinct signaling pathways." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 10, 1997, pages 6653-6662, XP002161387 ISSN: 0021-9258 abstract; figures 2,3 page 6658, column 2, line 22-26 ---	1-6, 29-41
X	SAMUEL D S ET AL: "Raf-1 activation stimulates proliferation and inhibits IGF-stimulated differentiation in L6A1 myoblasts." HORMONE AND METABOLIC RESEARCH, vol. 31, no. 2-3, February 1999 (1999-02), pages 55-64, XP000986726 ISSN: 0018-5043 the whole document ---	1-6, 29-41
A	DUDLEY DAVID T ET AL: "A synthetic inhibitor of the mitogen-activated protein kinase cascade." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 92, no. 17, 1995, pages 7686-7689, XP002161388 1995 ISSN: 0027-8424 cited in the application the whole document ---	1-6, 29-41
A	COLEMAN M E ET AL: "MYOGENIC VECTOR EXPRESSION OF INSULIN-LIKE GROWTH FACTOR I SIMULATES MUSCLE CELL DIFFERENTIATION AND MYOFIBER HYPERTROPHY IN TRANSGENIC MICE" JOURNAL OF BIOLOGICAL CHEMISTRY,US,AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, vol. 270, no. 20, 19 May 1995 (1995-05-19), pages 12109-12116, XP000611917 ISSN: 0021-9258 the whole document ---	1-41
A	US 5 444 047 A (DIPASQUALE GENE) 22 August 1995 (1995-08-22) the whole document ---	1-41
A	WO 97 45412 A (HEIMBROOK DAVID C ;STIRDIVANT STEVEN M (US); OLIFF ALLEN I (US); M) 4 December 1997 (1997-12-04) the whole document --- -/--	1-41

2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/17173

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/45 A61K31/352 A61K31/496 A61P21/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	ROMMEL CHRISTIAN ET AL: "Differentiation stage-specific inhibition of the Raf-MEK-ERK pathway by Akt." SCIENCE (WASHINGTON D C), vol. 286, no. 5445, 26 November 1999 (1999-11-26), pages 1738-1741, XP002161386 ISSN: 0036-8075 the whole document --- -/--	1-6, 29-41

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 February 2001	12/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Veronese, A

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	BOWEN D C ET AL: "Regulation of MuSK expression in skeletal muscle during development and after injury." SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 22, no. 1-3, 1996, page 1476 XP000986706 26th Annual Meeting of the Society for Neuroscience;Washington, D.C., USA; November 16-21, 1996 ISSN: 0190-5295 abstract	1-41

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/17173

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5444047 A	22-08-1995	NONE	
WO 9745412 A	04-12-1997	AU 3215197 A	05-01-1998
		EP 0934270 A	11-08-1999
		JP 2000508335 T	04-07-2000

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 January 2001 (18.01.2001)

PCT

(10) International Publication Number
WO 01/04354 A3

(51) International Patent Classification[7]: A61K 38/45, 31/352, 31/496, A61P 21/06

(21) International Application Number: PCT/US00/17173

(22) International Filing Date: 22 June 2000 (22.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/142,857 7 July 1999 (07.07.1999) US

(71) Applicant *(for all designated States except US)*: **REGENERON PHARMACEUTICALS, INC.** [US/US]; 777 Old Saw Mill River Road, Tarrytown, NY 10591-6707 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GLASS, David, J.** [US/US]; 341 Furnace Dock Road, #30, Cortlandt Manor, NY 10566 (US). **ROMMEL, Christian** [DE/CH]; Studio House, 4, route des Acacias, Les Acacias, CH-1227 Geneva (CH). **YANCOPOULOS, George, D.** [US/US]; 1519 Baptist Church Road, Yorktown Heights, NY 10598 (US).

(74) Agents: **PALLADINO, Linda, O.**; Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, NY 10591 et al. (US).

(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
16 August 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/04354 A3

(54) Title: USE OF RAS INHIBITORS OF INHIBITING MUSCLE ATROPHY

(57) Abstract: The present invention provides a method for inhibiting atrophy in muscle cells. It further provides a method for inhibiting skeletal muscle atrophy or causing skeletal muscle hypertrophy in vertebrate animals. It also provides a method of identifying agents, genes and gene products that may be used to reduce proteolysis or increase protein synthesis in muscle cells.

INTERNATIONAL SEARCH REPORT

.national Application No
PCT/US 00/17173

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/45 A61K31/352 A61K31/496 A61P21/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	ROMMEL CHRISTIAN ET AL: "Differentiation stage-specific inhibition of the Raf-MEK-ERK pathway by Akt." SCIENCE (WASHINGTON D C), vol. 286, no. 5445, 26 November 1999 (1999-11-26), pages 1738-1741, XP002161386 ISSN: 0036-8075 the whole document --- -/--	1-6, 29-41

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 February 2001	12/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Veronese, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

.national Application No
PCT/US 00/17173

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	COOLICAN SHARON A ET AL: "The mitogenic and myogenic actions of insulin-like growth factors utilize distinct signaling pathways." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 10, 1997, pages 6653-6662, XP002161387 ISSN: 0021-9258 abstract; figures 2,3 page 6658, column 2, line 22-26 ---	1-6, 29-41
X	SAMUEL D S ET AL: "Raf-1 activation stimulates proliferation and inhibits IGF-stimulated differentiation in L6A1 myoblasts." HORMONE AND METABOLIC RESEARCH, vol. 31, no. 2-3, February 1999 (1999-02), pages 55-64, XP000986726 ISSN: 0018-5043 the whole document ---	1-6, 29-41
A	DUDLEY DAVID T ET AL: "A synthetic inhibitor of the mitogen-activated protein kinase cascade." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 92, no. 17, 1995, pages 7686-7689, XP002161388 1995 ISSN: 0027-8424 cited in the application the whole document ---	1-6, 29-41
A	COLEMAN M E ET AL: "MYOGENIC VECTOR EXPRESSION OF INSULIN-LIKE GROWTH FACTOR I SIMULATES MUSCLE CELL DIFFERENTIATION AND MYOFIBER HYPERTROPHY IN TRANSGENIC MICE" JOURNAL OF BIOLOGICAL CHEMISTRY,US,AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, vol. 270, no. 20, 19 May 1995 (1995-05-19), pages 12109-12116, XP000611917 ISSN: 0021-9258 the whole document ---	1-41
A	US 5 444 047 A (DIPASQUALE GENE) 22 August 1995 (1995-08-22) the whole document ---	1-41
A	WO 97 45412 A (HEIMBROOK DAVID C ;STIRDIVANT STEVEN M (US); OLIFF ALLEN I (US); M) 4 December 1997 (1997-12-04) the whole document ---	1-41

-/—

2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/17173

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	BOWEN D C ET AL: "Regulation of MuSK expression in skeletal muscle during development and after injury." SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 22, no. 1-3, 1996, page 1476 XP000986706 26th Annual Meeting of the Society for Neuroscience;Washington, D.C., USA; November 16-21, 1996 ISSN: 0190-5295 abstract	1-41

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-5,7-38,40-41 relate to an extremely large number of possible compounds/methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds explicitly mentioned in the claims 6 and 39, (PD98059 and farnesyl transferase) and for the relationship between the mechanism of action disclosed in the application and skeletal muscle atrophy.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No
PCT/US 00/17173

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5444047 A	22-08-1995	NONE	
WO 9745412 A	04-12-1997	AU 3215197 A	05-01-1998
		EP 0934270 A	11-08-1999
		JP 2000508335 T	04-07-2000

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 17 April 2001 (17.04.01)	
International application No. PCT/US00/17173	**Applicant's or agent's file reference** REG 720-PCT
International filing date (day/month/year) 22 June 2000 (22.06.00)	**Priority date** (day/month/year) 07 July 1999 (07.07.99)
Applicant GLASS, David, J. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

25 January 2001 (25.01.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer R. Forax
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
N79990 DMG/TJD		

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/17173	22/06/2000	07/07/1999

International Patent Classification (IPC) or national classification and IPC
C12Q1/68

Applicant
REGENERON PHARMACEUTICALS INC

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25/01/2001	10.10.2001

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Knudsen, H

Telephone No. +49 89 2399 8696

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/17173

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-20	as originally filed

Claims, No.:

1-41	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-6,29-41(partially) (N,IS,IA), 7-9,19-21 (partially) (IA).

because:

☒ the said international application, or the said claims Nos. 1-6,29-33(fully), 7-9,19-21(partially) (IA) relate to the following subject matter which does not require an international preliminary examination (*specify*): **see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-6,29-41 (partially).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	9,11-33,40-41
	No:	Claims	1-8,10,34-39
Inventive step (IS)	Yes:	Claims	
	No:	Claims	9,11-33,40-41
Industrial applicability (IA)	Yes:	Claims	10-18,22-28,34-41

No: Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The International search of claims 1-6 and 29-41 was limited to the subject-matter of claims 6 and 39. As explained in the International Search Report the International Preliminary examination will be limited to the subject-matter searched.

The subject-matter of claims 1-6 and 29-33 and claims 7-9, 19-21, insofar as they concern the use of humans, relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document/s/:

D1: COOLICAN SHARON A ET AL: 'The mitogenic and myogenic actions of insulin-like growth factors utilize distinct signalling pathways.' JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 10, 1997, pages 6653-6662, ISSN: 0021-9258.

D2: SAMUEL D S ET AL: 'Raf-1 activation stimulates proliferation and inhibits IGF-stimulated differentiation in L6A1 myoblasts.' HORMONE AND METABOLIC RESEARCH, vol. 31, no. 2-3, February 1999 (1999-02), pages 55-64, ISSN: 0018-5043.

D3: DUDLEY DAVID T ET AL: 'A synthetic inhibitor of the mitogen-activated protein kinase cascade.' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 92, no. 17, 1995, pages 7686-7689, ISSN: 0027-8424 discloses the inhibitor PD098059 and its chemical formula [2-(2'-amino-3'-methoxyphenyl)-oxanaphthalen-4-one]

D4: MELISSA B RAMOCKI ET AL.: 'Signalling through mitogen-activated protein kinase and Rac/Rho does not duplicate the effects of activated Ras on skeletal myogenesis.' MOLECULAR and CELLULAR BIOLOGY, vol.17, 1997, p.3547-3555.

NOVELTY & INVENTIVE STEP:

5.1 Both D1 and D2 disclose that L6A1 muscle cells treated with IGF-1 and PD098059 shows a dramatic increase in differentiation and myogenesis both at morphological (myotube formation) and biochemical levels (eg creatine kinase activity) compared to cells treated with IGF-1 only. Thus, claims 1-6 and 34-39 lack novelty over D1 and D2.

5.2 Even if the claimed subject-matter was rendered novel over D1 and D2, it would not appear to involve an inventive step, because the present application only shows in an in-vitro assay that PD098059 is useful in increasing myogenesis. The application therefore does not contribute any medical teaching to what is taught in D1 and D2.

5.3 D4 discloses the transfection of C3H10 mouse fibroblast cells with constructs which lead to constitutive expression of Ras or Raf. The cells were treated with PD98059 and myogenesis was determined (see Fig.7). This test contains all of the elements of the method of present claims 7-8, 10 which therefore lacks novelty.

5.4 Claims 9 and 11-18 do not contain any features which render these claims inventive in view of the cited documents at present .

5.5 D3 discloses an in-vitro method for determining the activity of MEK protein in the presence of PD098059, in which the MEK activities in the presence and absence of PD098059 are compared. The said method differ from the method of claim 19 only in that the assay is carried out in muscle cells. However, the skilled person knows that the Ras ⇒ Raf-1 ⇒ MEK ⇒ MAPK pathway plays a role in muscle cells and it would therefore have been obvious to use muscle cells for the assay. Thus, claim 19 does not appear to be inventive.

5.6 The method of claim 20 differs from the method disclosed in D4 only in that a gene is introduced into the cell instead of a compound. Screening assays employing gene libraries are however well-known to the skilled person and the method of claim 20 therefore appears to be an obvious modification of the method of D4.

5.7 At present, the IPEA does not consider that dependent claims 21-28 contain any features which could render said claims inventive.

5.8 To the skilled person being informed in D1 and D2 that the inhibitor PD098059 enhances myogenesis in cell culture it would be obvious to use the said inhibitor in the treatment of muscular atrophy or to increase muscular hypertrophy in animals. Thus, claims 29-33 and 40-41 do not appear to be inventive.

INDUSTRIAL APPLICABILITY:

5.9 For the assessment of the present claims 1-6 and 29-34 and claims 7-9, 19-21, insofar as they concern the use of humans, on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

5.10 Claims 10-18, 22-28 and claims 34-41, insofar as they do not concern a therapeutic method, are considered industrially applicable.

Re Item VII

Certain defects in the international application

7.1 Contrary to the requirements of Rule 5(a)(ii) PCT, the closest prior art documents D1-D2 and D4 are not identified in the description and the relevant background art disclosed therein is not briefly discussed.

7.2 It is not possible to incorporate the teaching of a prior art document into the present application's disclosure by the expression "herein incorporated by reference" or equivalents thereof (cf PCT Guidelines, C-II, 4.17).

7.3 The first paragraph of the description is irrelevant to the present PCT application. The system of filing applications which are continuations-in-part of a prior application is not available in the PCT.

Re Item VIII

Certain observations on the international application

Though, the term "PD98059" is well-known in the field, it is preferable that it is mentioned in the claims by its chemical formula given in D3 in order that the claims are comprehensible from the wording of the claim alone (Guidelines C-III 4.2).